Medical Hypotheses 122 (2019) 120–123

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Retroperitoneal fibrosis. Steroid treatment response seems to depend on its association to IgG4 related disease

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ARTICLE INFO

Keywords:
IgG4 related disease
Retroperitoneal fibrosis
Steroids
IgG4
Tamoxifen

ABSTRACT

Retroperitoneal fibrosis (RF) is part of a rare fibrosclerotic disorder. Oral steroids are the initial treatment. Steroid combination with other immunosupressants is used in refractory cases. Steroids refractoriness has been observed in chronic cases. Some cases of RF represent a manifestation of the IgG4 related disease (IgG4-RD) that is associated to a dramatic response to steroid therapy. It is uncertain if RF́s treatment response differs according to its association with IgG4-RD. We hypothesize that RF́s treatment response to steroids depends on the association with IgG4-RD, thus, we collected and compared clinical data from 10 RF cases; 6 male, mean age 50.6 (± 16.15 SD) years. Mean FU was 28 (± 25.7 SD) months. According to IgG4 levels, patients were categorized as idiopathic RF (IRF n = 5) or RF-IgG4-RD (n = 5). Therapy response was categorized as complete, partial, stable disease, recurrence or non-response. Nine cases received initial therapy with prednisone; complete response was achieved in 4 RF-IgG4 RD. The remaining 5 cases (1 RF-IgG4RD and 4 IRF) underwent a 2nd line therapy; 4 prednisone + tamoxifen and 1 prednisone + azathioprine. Prednisone + tamoxifen combination achieved complete response in 1 case (RF-IgG4RD), partial response in 1 IRF; in 1 IRF case, disease remained stable and 1 did not respond. The prednisone + azathioprine treatment achieved complete response. At follow-up all patients remained stable and no recurrence was registered. These observations suggest and support the hypothesis that response to steroid monotherapy depends on the association of RF with IgG4, suggesting that IRF cases might benefit from initial combination therapies instead of steroid monotherapy.

Introduction

Retroperitoneal Fibrosis (RF) is a rare entity with an estimated prevalence of 1.38 cases per every 100.000 inhabitants [1].

RF is part of a rare fibrosclerotic disorder characterized by inflammation and fibrosis in multiple organs and is characterized by the presence of fibrosclerotic tissue in retroperitoneum and other abdominal structures and organs such as the abdominal aorta, celiac arteries, ureters among others. It has been suggested that such entities may be included under the term sclerosing mesenteritis [2].

RF can be classified as idiopathic RF (IRF) or secondary RF (SRF) to drugs, neoplasms, trauma, infections, surgeries and radiotherapy, with the former being the most frequently found [3].

Current knowledge and observations

Pathogenesis remains uncertain but observations suggest that it could be a consequence of a local inflammatory reaction to oxidized low-density lipoproteins (LDL) and ceroid mediated by B and T lymphocytes [4]. However, RF seems to be a manifestation of a systemic autoimmune disease rather than the result of local overexpression of fibro-inflammatory and atherosclerosis mechanisms [5,6].

Similar fibrosclerotic changes and clinical manifestations affecting different organs (especially the pancreas) have been reported to occur in the recently described IgG4 related systemic disease (IgG4 RD) that is characterized by elevated serum IgG4 levels, dense tissue infiltration by IgG4 positive plasma cells and storiform fibrosis. IgG4-RD may present as a tumor-like lesion affecting the pancreas and other organs even the retroperitoneal space and structures. IgG4RD shows a dramatic

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https://doi.org/10.1016/j.mehy.2018.11.005
Received 2 August 2018; Accepted 14 November 2018
0306-9877/

response to steroid therapy with evident significant improvement 4 to 12 weeks after steroids were started and only about 25% of cases relapse [2,7,8].

Interestingly, about 50% of initially presumed IRF cases represent a manifestation of the IgG4-RD, and are often associated to different autoimmune disorders and involvement to other organs [9].

RF treatment either for idiopathic or IgG4 RD is based on oral corticosteroids with most cases achieving good and sustained response rates. Refractory or recurrent cases are offered a second steroid trial or therapies such as tamoxifen (TMX), rituximab (RTX), azathioprine (AZA), cyclosporine (CYA), mofetil mycophenolate that are administered either as mono-therapy or in combination with steroids [7,10].

Most of current therapy information is limited and comes from small case series. Steroids as the first line therapy for RF are associated with a success or improvement rate of 40% but failure rates can be as high as 53% and relapse rates range between 12 and 30% [2,7,10].

There is scarce information on the factors that may predict failure or relapse after steroid treatment but an acute presentation manifested by an elevated C reactive protein and erythrocyte sedimentation rate (ESR), as well as imaging characteristics suggesting acute disease, have been associated to better response rates [7]. In the case of IgG4 RD, high pre and post treatment IgG4 serum levels are associated with relapse [11].

Hypothesis

It has been proposed that treatment failure appears frequently in those cases with a chronic presentation of the disease. It is not known at all if therapy response rates and outcomes differ according to the type of RF (IRF vs IgG4-RD). There is to our knowledge, only one small study assessing and comparing treatment outcomes in RF according to its relationship with IgG4 RD that showed no differences [9].

Considering the reported different response rates to steroid monotherapy and/or combined therapies between IgG4 RD and IRF [9,11], we hypothesize that IgG4-RD may represent a subgroup of patients with RF that will present a better response rate to standard treatment and will benefit from receiving initial steroid monotherapy, compared to those whit IRF that may represent a more refractory group in which the first line of therapy must entertain a combination of steroids and other immunosuppressant.

In order to test the hypothesis, that response or refractoriness to steroid therapy in RF could be linked to an association with IgG4-RD we conducted a retrospective and prospective study.

Material and methods

We included 10 cases of RF (mean age was 50.6 (± 16.15 SD) years; 6 male and 4 female). We found that RF mean age of onset of symptoms was of 46.3 years (± 14.7 SD) and mean age of diagnosis was of 47.7 (± 14.9 SD) years. The mean delay of diagnosis from the onset of symptoms was of 16.4 (± 14.9 SD) months. The most frequent symptom was abdominal pain (70%) followed by weight lost (40%). These patients were followed up for a mean time of 28 months (± 25.7 months SD).

RF diagnosis was established based on a 2fold increase above upper normal limit of serum IgG4, along with imaging and pathology findings. According to serum IgG4 levels, patients were categorized as IRF (normal IgG4 levels) or RF-IgG4 (2-fold increment above upper normal limit serum IgG4 subclass levels).

Endoscopic ultrasound (EUS) was performed only in those cases with pancreatic or peri-pancreatic abnormalities. Pathology specimens during diagnostic evaluation were obtained by EUS fine needle aspiration (FNA) or during surgical exploration. Plasma cell IgG4 infiltration was analyzed in 6 patients; 4 resulted IgG4 positive (IgG4+) after immunohistochemistry examination all of them with a 2 fold increment of serum IgG4.

Table 1
IRF: Idiopathic Retroperitoneal Fibrosis; IgG4 RD: IgG4 related disease RF; OOI: other organ involvement.

Case	Hydronephrosis	Renal function	JJ stenting	OOI
IRF	no	preserved	no	no
IgG4 RD	no	preserved	no	Pancreas
IRF	Unilateral	decreased	yes	no
IRF	no	preserved	no	no
IRF	no	preserved	no	no
IgG4 RD	Unilateral	decreased	yes	Pancreas
IgG4 RD	no	preserved	no	Pancreas
IgG4 RD	no	preserved	no	Pancreas
IgG4 RD	Bilateral	decreased	yes	no
IRF	no	preserved	no	no

Response to therapy was considered complete when RF related symptoms and/or imaging findings totally disappeared at the last FU visit after therapy was initiated. The response was deemed as partial when symptoms and/or imaging findings persisted but to a lesser intensity or quantity (< 50%) compared to base line as reported by the patient and radiology reports. The disease was considered stable when RF related symptoms and/or imaging abnormalities remained unchanged. Non-responders were those patients in which clinical and/or imaging symptoms and/or characteristics worsened or progressed despite therapy.

Diagnostic and FU evaluation included general blood work, IgG4 serum levels, abdominal computed tomography (CT) scan or magnetic resonance (MRI). Hydronephrosis was observed in 3 cases (2 IgG4 RD RF) all showing decreased renal function based on urinary output (< 500 ml/day) and/or creatinine levels (> 1.3 mg/dl). In all cases a JJ stent was placed (unilaterally in 2 cases and bilaterally in 1) table 1. None of the 10 cases presented with an inflammatory abdominal aortic aneurysm (IAAA) either at onset or during FU. Four cases with IgG4 RD presented with pancreas involvement Table 1.

Therapy outcomes in IRF and IgG4 RD RF

Prednisone monotherapy

Initial monotherapy with prednisone (PDN) consisted in administering 40 mg/qd during 4 weeks followed by a progressive decrement of 5 mg per week the following 8 weeks, and it was administered to 5 RF-IgG4 and 4 IRF cases. One case with IRF did not receive any treatment, due to the absence of symptoms and image stability.

After this first steroid monotherapy trial, the overall (IRF + RF-IgG4) response rate was 40%. When comparing groups according to IgG4 RD levels, a complete response (clinical and image) was achieved in 4 (80%) cases with RF-IgG4 and in none (0%) of the 4 IRF cases that together with the remaining RF-IgG4 RD case, were deemed non-respondent, and underwent a 2nd line treatment.

Second line treatment

In those steroid refractory cases a prednisone (PDN) + tamoxifen (TMX) trial (3 IRF and 1 IgG4 RD RF) or PDN + azathioprine (One case with IRF) trial were offered.

Combination therapy with PDN (new cycle of 40 mg for 1 month and progressive reduction) + TMX (10 mg daily) achieved a complete response in 1 RF-IgG4 case; from the 3 IRF cases, 1 had partial response, in 1 the disease remained stable and 1 persisted as not respondent as abdominal pain lingered.

The only case with IRF that received PDN (same dosage as before) + azathioprine (50 mg/day for 3 months then 100 mg/day) achieved complete clinical and imaging response.

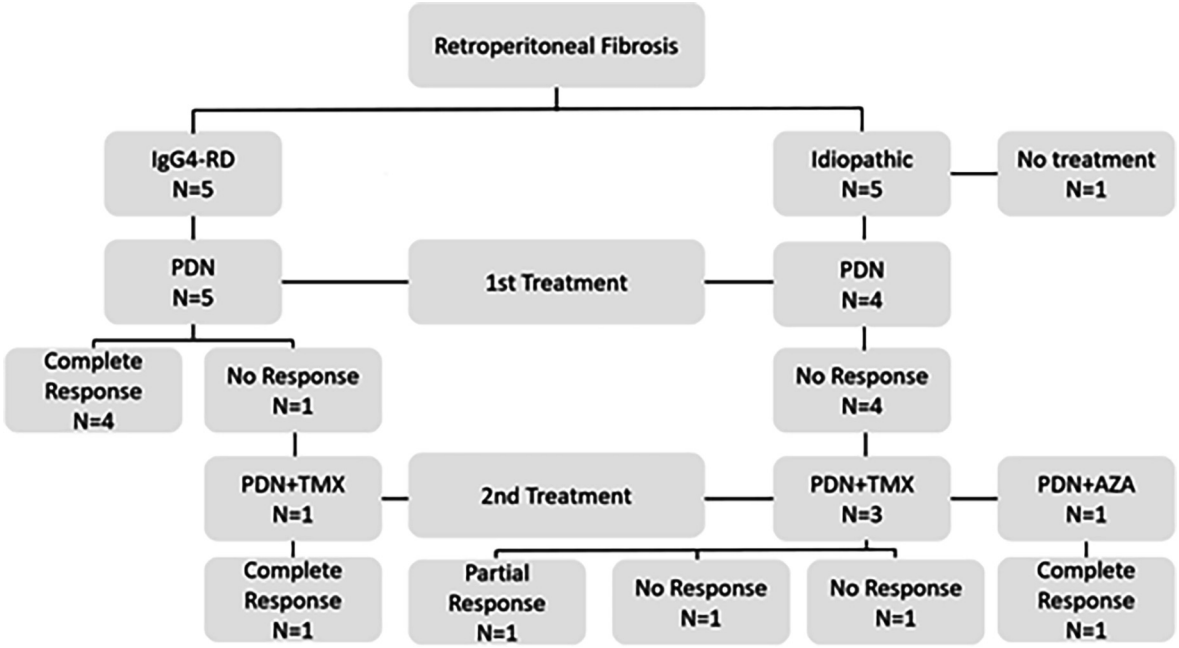

Fig. 1. Patient clinical and imaging outcomes according to treatment.

Follow up

After a mean FU of 28 months, (range 6–84) the 6 complete responders have remained asymptomatic as those with partial response. In 2 cases (1 with no treatment and 1 that received PDN + TMX) disease remained stable with no clinical symptoms but imaging persistence. No recurrence has been registered. Abdominal pain in the non-respondent case is being controlled by our institution's pain clinic Fig. 1.

Discussion

RF associated to IgG4 RD compared to IRF, resulted in better outcomes and higher response rate to prednisone monotherapy (RF-IgG4 80% vs. IRF 0%), regrettably, benefit from combination of PDN + TMX or AZA was limited with only 50% of steroid refractory cases showing either complete or partial response.

Similar response rates for RF have been reported, and some of them have suggested that refractoriness to steroid monotherapy might depend on the chronicity of the disease [12]. Acute RF usually presents with elevated C reactive protein and/or ESR as well as with subtle imaging changes; all together have been associated to better response and lesser recurrence rates to steroid monotherapy. Chronic presentation cases may represent or be associated to steroid refractoriness and have been offered different combination therapies that include TMX and AZA among others with different success rates [13–15]. The rationale behind the use of TMX rests in the fact that it increases the production of transforming growth factor beta and has been proposed to decrease inflammation and to have modulating growth effects that may benefit those chronic inflammatory states. It has been reported that the PDN + TMX combination as first or 2nd line treatment after failure to surgery and/or PDN monotherapy, achieves total response in up to 60% of cases, although in our series the overall success was lower (25%). Other therapies such as AZA, colchicine, thalidomide, and methotrexate with different immunosuppressive, anti-fibrotic and anti-angiogenic effects have been tried but information is scarce.

It is unclear but provocative if responsiveness may be related to the presence or absence of IgG4-RD. Similar to different reports on therapy outcomes for any IgG4 RD manifestation, all our RF-IgG4-RD cases responded to either steroid monotherapy (80%) or combination (20%) therapy [16]. Nevertheless, there are several reports of steroid refractoriness in IgG4RD, especially in autoimmune pancreatitis. In such cases rituximab has represented a good therapeutic option. Interestingly, the presentation time and form (acute or chronic) has never been considered as a potential cause of such lack of response, instead pre and post IgG4 levels have been considered as a potential prognostic factor for therapy response.

We are not clear if the lack of response to PDN monotherapy and to PDN + TMX combination therapy in the IRF cases may be related to TMX dosage or to other aspects of the disease such as its chronicity, which as mentioned before has been related to a lack of response.

We were not able to establish if any of our cases (idiopathic or IgG4 RD) presented in an acute or chronic stage, but according to our findings, it can be hypothesized that IgG4-RD cases may represent or present in a more acute way compared to IRF or simply IgG4-RD has a different pathogenesis compared to IRF that may explain its higher steroid responsiveness.

We are aware that due to the uncontrolled and retrospective nature of the study as well as the small number of patients and lack of clinical or imaging information to assess the chronicity or not of each case our findings should be taken cautiously.

In conclusion, our results suggest that IgG4-RD should be considered in any RF case since its presence may modify treatment choices. RF presenting as a manifestation of IgG4-RD shows a higher response rate to initial steroid monotherapy compared to IRF cases that may benefit from initial combination therapies. The best combination therapy remains unclear as well as the factors (chronic presentation, IgG4 RD, etc.) involved in the response to different therapies. Both are questions that deserve further research.

Disclosures

None of the enlisted authors has any conflict of interest or financial relationships to disclose.

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